REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the amendments and remarks herein.

Claims 1-53 are pending in the application. New claims 52-53 have been added by this amendment. Support for the new claims may be found throughout the specification and in the original claims, particularly on pages 6-10. Claims 1 and 48 have been amended to clarify that the hydrogel matrix is administered in liquid form. This amendment is supported throughout the specification, such as on pages 5 and 10-11. Additionally, Claims 32 and 48 has been amended to clarify that polar amino acids can be present in a mixture. Further, Claim 48 has been amended to remove aminoguanidine, which is a less preferred optional ingredient of the matrix. Applicant submits that no new matter is introduced by this amendment.

I. 102(b) Rejection

Claims 1-6, 16-17, 28 and 31 stand rejected as being anticipated by WO 98/55161 to Schacht *et al.* The office relies upon the Schacht reference as disclosing a biopolymer matrix comprising a crosslinked gelatin/polysaccharide composition used in the form of a wound dressing. Applicant respectfully traverses this rejection.

Claim 1, and all claims dependent thereon, recite that the hydrogel matrix is administered in liquid form to the ulcer. As clearly stressed in the present application, the preferred method of administration is by injection in and around the area of the ulcer. The cited reference is directed to a solid matrix composition that is applied in the form of a film, foam, fibers woven into tissue, etc. The Schacht reference does not suggest application of the matrix described therein in liquid form. As a result, Applicant respectfully requests reconsideration and withdrawal of this rejection.

II. Obviousness Rejections

Claims 1-10, 14, 16-28, 31-35, 37-44, and 46 stand rejected under U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,824,331 to Usala in view of the Jude reference and the

Miller reference. The Office relies upon the Usala reference as disclosing a hydrogel matrix that can promote vascularization. The Office relies upon the Jude reference as suggesting that nitric oxide and nitric oxide synthase have a deleterious effect on diabetic foot ulcers. The Miller reference is relied upon as suggesting that ischemic diabetic foot ulcers can be treated by "vascular repair." Applicant respectfully traverses this rejection.

As noted in the Office Action, the '331 patent is entirely silent as the treatment of any sort of ulcer. Rather, the Usala reference is directed to a device for release of hormones. The '331 patent merely suggests, as noted in Example 8, that the matrix composition resulted in microvascular formation around an intramuscular transplant.

The Office relies upon the combination of the Miller and Jude references as providing motivation to use the matrix described in the '331 patent in the treatment of a diabetic foot ulcer. However, these references actually fail to provide any suggestion that might lead one of ordinary skill in the art to the presently claimed invention. The Jude reference merely concludes that selective suppression of *i*NOS activity might be beneficial in the treatment of diabetic foot ulcers. However, the Jude reference also cautions that suppression of *i*NOS could result in promotion of infection as NO is crucial to host defense. At most, the Jude reference is an invitation to experiment with NOS inhibitors. There is no experimental data in the Jude reference regarding the successful use of any treatment protocol for diabetic foot ulcers. The reference merely suggests a correlation between *i*NOS activity and diabetic foot ulcers, and concludes that suppression of *i*NOS might be beneficial in the treatment of such ulcers. However, the reference also suggests possible deleterious effects of suppression of NO and provides absolutely no guidance as to what type of "NOS inhibitor" might be a successful treatment option. Thus, one of ordinary skill in the art would view the Jude reference as nothing more than an invitation to experiment, and certainly not a reference that, in combination with the '331 patent and the Miller reference, would render the claimed invention obvious.

Additionally, we note that independent Claims 1, 32, 48, and 52, are all directed to a method of treating an ulcer involving administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate. There is no suggestion in the '331 patent that such ingredients are NOS inhibitors. Thus, even if one were to consider the Jude reference as suggestive of the use of

a NOS inhibitor in the treatment of a diabetic foot ulcer, the combination of Jude with the '331 patent would still not result in Applicants' claimed invention because neither reference suggests that gelatin or long chain carbohydrates are considered NOS inhibitors.

The Miller reference similarly fails to provide any motivation or suggestion that would lead one to utilize the hydrogel matrix of the '331 patent in the treatment of a diabetic foot ulcer. The Miller reference, a full copy of which is enclosed for reference by the Examiner, stresses the need for separate treatment protocols for the two main classes of diabetes-related ulcers; namely, ischemic ulcers and neuropathic ulcers. The Miller reference describes the ischemic ulcer as "secondary to vascular compromise" and notes that "without reconstructive vascular surgery," the chances of healing is poor and amputation inevitable (page 759, second column, first full paragraph) (emphasis added). Similarly, the Miller reference suggests that an ischemic foot can be treated with vein graft reconstruction (page 760, first paragraph).

With respect to neuropathic ulcers, the Miller reference actually teaches away from vascularization-related treatments by suggesting that it is mistaken to consider occlusive small vessel disease as having a significant role in chronic nonhealing neuropathic ulcers (page 759, last paragraph). Miller suggests that "intrinsic microvascular disease" is not a major etiologic factor in the neuropathic foot (page 760, first paragraph).

Thus, the Miller reference merely suggests that in certain ulcers, specifically ischemic ulcers, vascular repair in the form of reconstructive vascular surgery is required to avoid amputation. For the treatment of neuropathic ulcers, the Miller reference suggests tissue debridement and relief from pressure at the site of the ulcer and teaches away from vascular-related therapies.

The '331 patent suggests that the matrix described therein can promote formation of microvasculature. However, the Miller reference fails to teach or suggest that a treatment involving microvascular formation would be suitable for ulcer treatment. With respect to neuropathic ulcers, the Miller reference expressly discounts the suggestion that microvascular disease is an etiologic factor and, thus, teaches away from vascular-related treatments. The "vascular repair" language relied upon by the Examiner is only used by Miller in reference to the treatment of ischemic ulcers secondary to major vascular compromise in the foot. Miller stresses

that the type of vascular repair that is required is reconstructive vascular surgery, and there is nothing in the Miller reference that would suggest that a microvasculature-forming matrix would be helpful in the least. Thus, there is no teaching or suggestion in the Miller reference, when considered singly or in combination with the '331 patent and/or the Jude reference, that a matrix comprising gelatin and a long chain carbohydrate would be suitable for ulcer treatment. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claims 1-51 stand rejected under U.S.C. §103(a) as being unpatentable over WO 00/02999 to Usala in view of the Miller reference. Similarly, Claims 1-51 stand rejected as unpatentable over U.S. Patent No. 6,231,881 in view of the Miller reference. As with the previous rejection, the Examiner relies upon the Miller reference as providing the motivation to use the matrix described in the Usala references in the treatment of a diabetic foot ulcer. Specifically, the Examiner states that it would have been obvious to use the compositions in the Usala patent applications in the treatment of a diabetic foot ulcer because "therapy for diabetic foot ulcers include vascular repair of tissue." Applicants respectfully traverse these rejections.

As noted above, the Miller reference defines "vascular repair" as reconstructive vascular surgery, and only suggests that such a treatment method would be successful for ischemic ulcers. With respect to neuropathic ulcers, the Miller reference actually teaches away from a microvascular-related treatment since the Miller reference suggests that intrinsic microvascular disease is not a major etiologic factor in such ulcers. Thus, it is clear the Miller reference only suggests that, for a certain kind of ulcer, treatment may include vascular repair in the form of reconstructive vascular surgery to restore blood flow to the foot. There is nothing in the Miller reference to suggest that a composition that induces microvasculature formation would be a successful treatment option for any kind of diabetes-related ulcer. Accordingly, Applicant respectfully submits that the Office is reading the term "vascular repair" far too broadly in light of the full teachings of the Miller reference. As a result, Applicant respectfully requests reconsideration and withdrawal of these rejections.

III. Obviousness-type Double Patenting Rejecting

Claims 1-29, 31-42, 46-48, and 50-51 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-57 of U.S. Patent No. 6,261,587 in view of the Miller reference. Again, the Examiner relies upon the Miller reference as suggesting the treatment of diabetic foot ulcers using "vascular repair" and concludes that it would have been obvious to use the claimed vascularization method of the '587 patent in the treatment of such ulcers. Applicant respectfully traverses this rejection.

Again, as noted above, the Miller reference actually defines vascular repair as reconstructive vascular surgery, and does not suggest that a composition capable of forming microvasculature would be suitable for the treatment of any type of diabetes-related ulcer. One of ordinary skill in the art would not view a composition designed to promote the growth of localized microvasculature as equivalent to, or a replacement for, reconstructive vascular surgery designed to restore adequate blood flow to an appendage. There is nothing in Miller to suggest that the severe vascular compromise that is characteristic of ischemic ulcers would be overcome by localized microvasculature at the site of the ulcer. Instead, the clear teachings of the Miller reference indicate that reconstructive surgery is required to correct such a condition. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

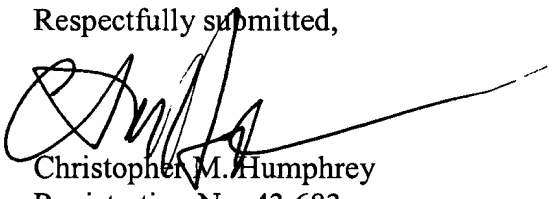
IV. Consideration Of Previously Submitted Information Disclosure Statements

It is noted that an initialed copy of the PTO 1449 Forms that were submitted with Applicants' Information Disclosure Statements filed October 30, 2001, April 3, 2002, and May 18, 2004 have not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed copy of these Form 1449's be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statements and the Form 1449's are attached hereto. Copies of the cited references were provided at the time of filing the original Information Disclosure Statements, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

It is believed that all pending claims are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned should the Examiner have any comments or suggestions in order to expedite examination of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



Christopher M. Humphrey
Registration No. 43,683

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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Polly P. Burton

Polly P. Burton

Attorney's Docket No. 35626/234825

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Anton-Lewis Usala		
Appl. No.:	09/870,414	Group Art Unit:	1614
Filed:	May 30, 2001	Examiner:	To Be Assigned
For:	METHOD OF TREATING CHRONIC ULCERS		

October 30, 2001

Box Missing Parts
Commissioner for Patents
Washington, DC 20231

INFORMATION DISCLOSURE STATEMENT
CITATION UNDER 37 C.F.R. § 1.97

Sir:

Attached is a list of documents on form PTO-1449 together with a copy of each identified document. It is requested that the Examiner consider these documents and officially make them of record in accordance with the provisions of 37 C.F.R. § 1.97 and Section 609 of the MPEP. By submitting the listed documents, Applicant in no way makes any admission as to the prior art status of the listed documents, but is instead submitting the listed documents for the sake of full disclosure.

Respectfully submitted,

Christopher M. Humphrey
Registration No. 43,683

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Box Missing Parts, Commissioner For Patents, Washington, DC 20231, on October 30, 2001.

Tracey S. Wright

Tracey S. Wright

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	09/870,414
Filing Date	May 30, 2001
First Named Inventor	Usala
Group Art Unit	1614
Examiner Name	To Be Assigned
Attorney Docket Number	35626/234825

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant Of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages of Relevant Figures Appear
	1	4,198,479		Tytell *et al.*	04-15-1980	Whole Document
	2	4,520,821		Schmidt *et al.*	06-04-1985	Whole Document
	3	4,657,866		Kumar	04-14-1987	Whole Document
	4	4,696,286		Cochrum	09-29-1987	Whole Document
	5	4,797,213		Parisius *et al.*	01-10-1989	Whole Document
	6	4,902,295		Walthall *et al.*	02-20-1990	Whole Document
	7	4,950,483		Ksander *et al.*	08-21-1990	Whole Document
	8	4,957,902		Grinnell	09-18-1990	Whole Document
	9	5,021,349		Drouet *et al.*	06-04-1991	Whole Document
	10	5,079,160		Lacy *et al.*	01-07-1992	Whole Document
	11	5,128,360		Cerami *et al.*	07-07-1992	Whole Document
	12	5,246,971		Williamson *et al.*	09-21-1993	Whole Document
	13	5,263,983		Yoshizato *et al.*	11-23-1993	Whole Document
	14	5,322,790		Scharp *et al.*	06-21-1994	Whole Document
	15	5,358,969		Williamson *et al.*	10-25-1994	Whole Document
	16	5,457,093		Cini *et al.*	10-10-1995	Whole Document
	17	5,591,709		Lindenbaum	01-07-1997	Whole Document
	18	5,605,938		Roufa *et al.*	02-25-1997	Whole Document
	19	5,645,591		Kuberasampath *et al.*	07-08-1997	Whole Document
	20	5,716,404		Vacanti *et al.*	02-10-1998	Whole Document
	21	5,824,331		Usala	10-20-1998	Whole Document
	22	5,830,492		Usala	11-03-1998	Whole Document
	23	5,834,005		Usala	11-10-1998	Whole Document
	24	5,840,059		March *et al.*	11-24-1998	Whole Document
	25	5,852,009		Cerami *et al.*	12-22-1998	Whole Document
	26	5,855,617		Orton	01-05-1999	Whole Document
	27	09/766,330		Usala	01-19-2001	Whole Document
	28	6,261,587		Usala	07-17-2001	Whole Document
	29	6,231,881		Usala *et al.*	05-15-2001	Whole Document

Examiner Signature		Date Considered	

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. RTA 2103478v1

[1] Unique citation designation number.
[2] See attached Kinds of U.S. Patent Documents.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 3

Complete if Known	
Application Number	09/870,414
Filing Date	May 30, 2001
First Named Inventor	Usala
Group Art Unit	1614
Examiner Name	To Be Assigned
Attorney Docket Number	35626/234825

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Office[3]	Number[4]	Kind Code (if known)[5]	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	30		0 213 908	A2	Hana Biologics, Inc.	03-11-1987	Whole Document	
	31	WO	91/09119	A1	Trancel Corporation	06-27-1991	Whole Document	
	32	WO	92/19195		Brown University Research Foundation	11-12-1992	Whole Document	
	33	EP	0 526 756	A	C.R. Bard, Inc.	02-10-1993	Whole Document	
	34	WO	93/16685		Encelle, Inc.	09-02-1993	Whole Document	
	35	EP	0 564 786	A	Lifecell Corp.	10-13-1993	Whole Document	
	36	WO	93/24112	A1	Clover Consolidated, Limited	12-09-1993	Whole Document	
	37	WO	94/03154	A1	Washington University	02-17-1994	Whole Document	
	38	WO	94 08702		University of Utah	04-28-1994	Whole Document	
	39	WO	94/15589	A1	Clover Consolidated, Limited	07-21-1994	Whole Document	
	40	WO	95/14037		Ibah, Inc.	05-26-1995	Whole Document	
	41	WO	95/19430	A1	The Rogosin Institute	07-20-1995	Whole Document	
	42	DE	44 31 598	A1	Sittinger, Michael	03-07-1996	Whole Document	
	43	WO	97/20569	A	Encelle, Inc.	06-12-1997	Whole Document	
	44	WO	97 39107		The Governors of the University of Alberta	10-23-1997	Whole Document	
	45	EP	0 363 125	A2	Hana Biologics, Inc.	10-02-1998	Whole Document	
	46	WO	00/02999	A2	Encelle, Inc.	01-20-2000	Whole Document	

Examiner Signature		Date Considered	

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. RTA 2103478v1

[3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	09/870,414
				Filing Date	May 30, 2001
				First Named Inventor	Usala
(Use as many sheets as necessary)				Group Art Unit	1614
				Examiner Name	To Be Assigned
Sheet	*3*	Of	*3*	Attorney Docket Number	35626/234825

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s) , volume-issue number(s), publisher, city and/or country where published.	T
	47	HUBBELL *et al.*, "Tissue Engineering," *Chemical & Engineering News,* (March 13, 1995), pp. 42-54.	
	48	ISNER *et al.*, "Therapeutic Angiogenesis," *FRONTIERS IN BIOSCIENCE*, Vol. 3 (May 5, 1998) pp. 49-69.	
	49	PENNISI *et al.*, "Mice Null for *Sox18* Are Viable and Display a Mild Coat Defect", *Molecular and Cellular Biology*, December 2000, pp. 9331-9336, Vol. 20, No. 24.	
	50	RAMSEY *et al.*, "Incidence, Outcomes, and Cost of Foot Ulcers in Patients with Diabetes", *Diabetes Care*, March 1999, pp. 382-387, Vol. 22, No. 3.	
	51	RAVIN *et al.*, "Long- and Short-Term Effects of Biological Hydrogels on Capsule Microvascular Density around Implants in Rats", *Neovascularization in Capsules*, April 12, 2001, pp. 313-318.	

Examiner Signature		Date Considered	

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. RTA 2103478v1

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Attorney's Docket No. 35626/234825

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Anton-Lewis Usala	Confirmation No.:	7087
Appl. No.:	09/870,414	Group Art Unit:	1614
Filed:	May 30, 2001	Examiner:	To Be Assigned
For:	METHOD OF TREATING CHRONIC ULCERS		

April 3, 2002

Commissioner for Patents
Washington, DC 20231

SUPPLEMENTAL CITATION UNDER 37 C.F.R. § 1.97

Sir:

Attached is a Supplemental Form PTO-1449 listing several documents, including several references cited in the International Search Report for the corresponding International Application Number PCT/US01/17387, not more than three months prior to the filing of this Statement. A copy of each document, including the Search Report, is enclosed. It is requested that the Examiner consider these documents and officially make them of record in accordance with the provisions of 37 C.F.R. § 1.97 and Section 609 of the MPEP. By submitting the listed documents, Applicant in no way makes any admission as to the prior art status of the listed documents, but is instead submitting the listed documents for the sake of full disclosure.

Respectfully submitted,

Christopher M. Humphrey
Registration No. 43,683

CUSTOMER NO. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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Tracey S. Wright

Tracey S. Wright – RTA 2114751v1

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Substitute for form 1449A/PTO
(Revised 10/2001)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	09/870,414
Filing Date	May 30, 2001
First Named Inventor	Anton-Lewis Usala
Group Art Unit	1614
Examiner Name	To Be Assigned
Attorney Docket Number	35626/234825

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number Number - Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee of Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages of Relevant Figures Appear
	52	6,132,759	10-17-2000	Schacht *et al.*	
	53	6,197,330	03-06-2001	Rees *et al.*	
	54	6,299,898	10-09-2001	Rees *et al.*	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Country Code - Number Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	55	WO 93/16717 A1	09-02-1993	The Rockefeller University		
	56	WO 98/55161 A1	12-10-1998	Innogenetics N.V.		
	57	WO 00/02596 A1	01-20-2000	Encelle, Inc.		

Examiner Signature		Date Considered	

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. RTA 2114753v1

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Attorney's Docket No. 035626/234825 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	Anton-Lewis Usala	Confirmation No.:	7087
Appl. No.:	09/870,414	Art Unit:	1614
Filed:	May 30, 2001	Examiner:	To Be Assigned
For:	METHOD OF TREATING CHRONIC ULCERS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
CITATION UNDER 37 C.F.R. § 1.97

Sir:

Attached is a list of documents on form PTO-1449 together with a copy of each identified document. It is requested that the Examiner consider these documents and officially make them of record in accordance with the provisions of 37 C.F.R. § 1.97 and Section 609 of the MPEP. By submitting the listed documents, Applicant in no way makes any admission as to the prior art status of the listed documents, but is instead submitting the listed documents for the sake of full disclosure.

It is not believed that any fees are necessary to allow consideration of this paper. However, if any fees are due, Applicant hereby authorizes any fees to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Christopher M. Humphrey
Registration No. 43,683

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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Tracey S. Wright

Tracey S. Wright – RTA 2155196v1

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Substitute for form 1449A/PTO
(Revised 10/2001)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	09/870,414
Filing Date	May 30, 2001
First Named Inventor	Anton-Lewis Usala
Group Art Unit	1614
Examiner Name	To Be Assigned
Attorney Docket Number	35626/234825

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number Number - Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee of Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages of Relevant Figures Appear
	58	6,046,160	04-04-2000	Obi-Tabot	
	59	6,238,888 B1	05-29-2001	Gentz *et al.*	
	60	6,372,494 B1	04-16-2002	Naughton *et al.*	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Country Code - Number Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T

Examiner Signature		Date Considered	

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. RTA 2155197v1

Essentials of Pressure Ulcer Treatment

The Diabetic Experience

O. FRED MILLER III, MD

BACKGROUND. *Diabetes accounts for over half of the lower extremity amputations in the United States. However, ulcers of the diabetic foot can often be treated successfully and amputations avoided.*

OBJECTIVE. *To review treatment of diabetic foot ulcers.*

RESULTS. *Physicians must recognize the critical clinical and diagnostic features of ischemic and neuropathic ulcers. Therapy is directed towards vascular repair in the ischemic ulcer and relief of weight bearing through casting and shoes with molded insoles in the neuropathic ulcer. Sound principles of wound care apply to all ulcers.*

CONCLUSION. *For successful preventive foot care patients and physicians need to understand how and why ulcers form and the rationale for the types of footwear and care necessary to prevent ulcers.* J Dermatol Surg Oncol 1993;19:759–763.

Diabetes accounts for more than half of the lower extremity amputations in the United States. In 1987 the cost of lower extremity amputations in diabetics approximated one half billion dollars.[1] It is estimated that foot care programs could reduce amputations by 44 to 85%.[2] To reduce and prevent amputations and the attendant morbidity, mortality, and cost, the dermatologist must have an understanding of the pathogenesis of diabetic foot ulcers and be competent in teaching patients foot care preventive medicine.

Two distinctive types of diabetic ulcers can be identified: neuropathic and ischemic. Although components of neuropathy and ischemia might be seen in the same patient, most ulcerations have a predominant etiologic factor and characteristic clinical features with therapy directed effectively towards either the compromised blood supply or the neuropathy. Infection may be a significant complicating factor in either type of ulcer. Specific cutaneous signs of diabetes, eg, necrobiosis lipoidica diabeticorum, idiopathic bullae, and diabetic dermopathy, are not noted with increased frequency with either type of ulcer.

The ischemic ulcer secondary to vascular compromise appears in the setting of signs of a cool foot, dependent rubor, pallor on elevation, atrophic shiny skin, and diminished-to-absent dorsalis pedis and/or posterior tibial pulses and symptoms of intermittent claudication and leg pain in the supine position eased by dependency (Figure 1). Without reconstructive vascular surgery the prognosis for healing is poor and amputation inevitable. If the occlusive vascular disease is correctable, the ulcer will generally heal quickly with basic wound care after surgery.

The neuropathic ulcer is essentially a pressure ulcer in an individual with absent or distorted foot sensation. Although most commonly seen with diabetes, morphologically similar pressure ulcers can be seen associated with other neuropathies, eg, familial neuropathy, leprosy, tabes dorsalis, and various neurological syndromes. Neuropathic ulcers, located over pressure points, especially the first and fifth metatarsal heads and great toes, are classically well circumscribed with surrounding exuberant white callus-like material (Figure 2). The asymptomatic insensate foot has normal temperature and color and usually strong pulses. Neurologically, touch, pressure, and proprioception are impaired or lost.

Neuropathy affects not only sensory, but also motor and autonomic nerves. Motor neuropathy leads to denervation of small foot muscles. As muscles weaken and waste, foot bone relationships are altered, resulting in hammer toes, claw toes, pes cavus deformity, and abnormal bony pressure points with increased weight bearing over the metatarsal heads.[3] Autonomic nerve involvement accounts for the dryness, scaling, and fissuring associated with decreased sweating. Patients with sympathetic neuropathy can develop Charcot foot, the distinctive model of the joint-destructive, bone-fracturing process in the insensate foot. The warm foot with sympathetic neuropathy presents with edema, hyperemia, and an intact circulation. Within a few weeks or many months midfoot bone and joint destruction leaves a permanent variably deformed foot (Figure 2).[4]

The common mistaken opinion that occlusive small vessel disease plays a significant role in nonhealing neuropathic ulcers can result in unnecessary amputations.

From the Department of Dermatology, Geisinger Clinic, Danville, Pennsylvania.

Address correspondence and reprint requests to: O. Fred Miller III, MD, Director, Department of Dermatology, Geisinger Clinic, Danville, PA 17822.

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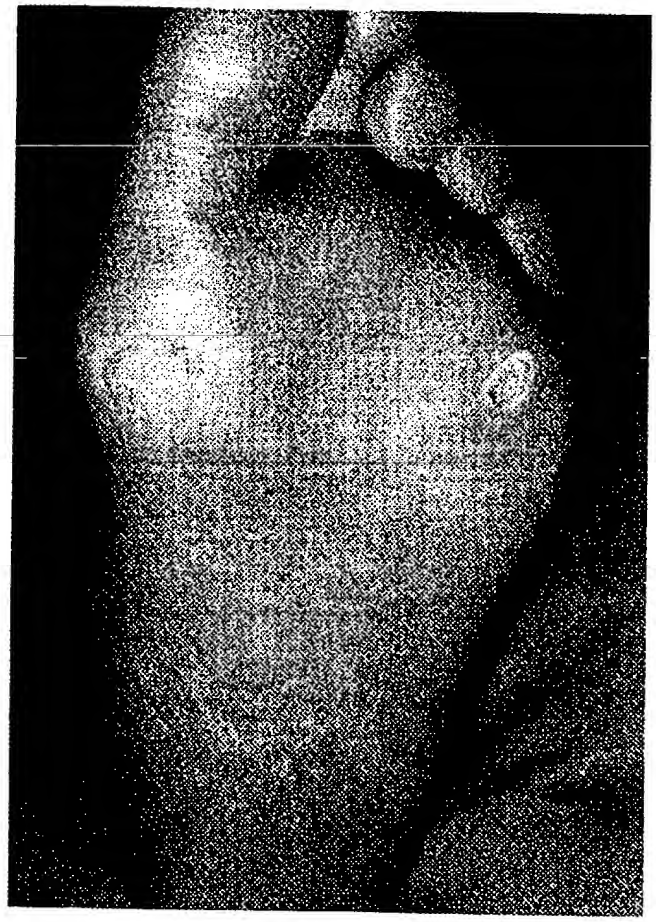


Figure 1. Ischemic ulcer in foot with dependent rubor and reduced pulses.

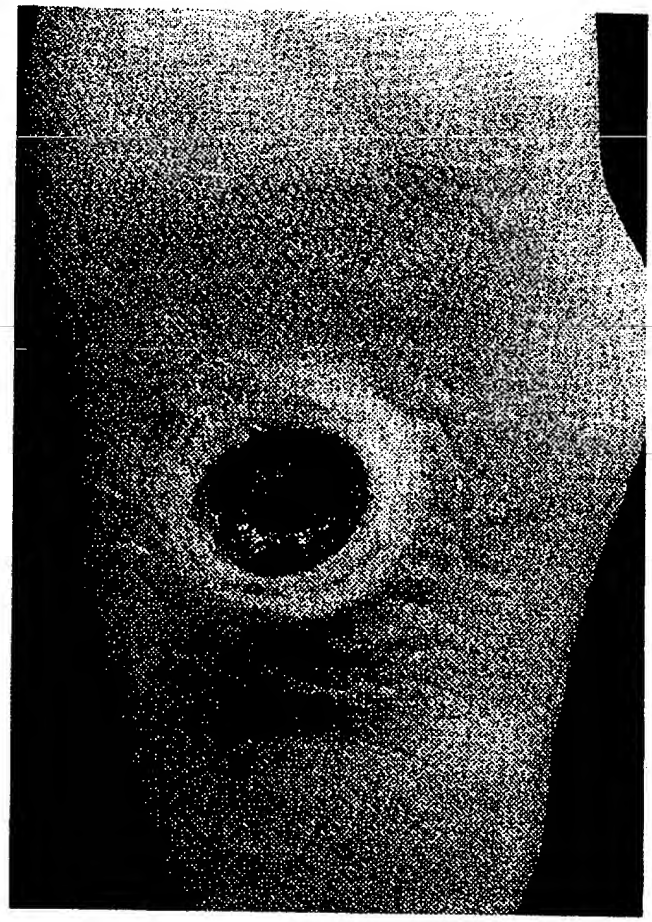


Figure 2. Neuropathic ulcer with callus on insensate, deformed (Charcot) foot.

Intrinsic microvascular disease is not a major etiologic factor, although large vessel disease can account for ischemia in the neuropathic foot. Atherosclerosis occurs most commonly in the femoropopliteal segment. In diabetics a higher incidence of tibial and peroneal artery occlusion is seen. A diabetic with an ischemic foot and strong popliteal pulse must be evaluated for tibial artery occlusion and possible vein graft reconstruction from the popliteal artery to either the dorsalis pedis or posterior tibial arteries.[5]

Brand's studies[6] demonstrate how an insensate foot with good blood supply may suffer local ischemia and tissue breakdown from the continuous low pressure of ill-fitting shoes, the trauma from foreign objects and most commonly from just the repetitive moderate stresses of everyday walking. In an individual with intact foot sensation, the perception of tenderness and changing thresholds of foot pain lead to conscious or unconscious alterations in gait, discontinuation of activity, or removal of footwear. In contrast, the individual with an asymptomatic insensate foot will not be aware of the warning signals of early inflammation and can continue walking on a pressure point until local inflammation is followed by tissue damage and, eventually, ulceration.

Neurologic and vascular evaluation of the insensate foot with or without ulceration involves the potential consultation and collaboration of a large group of specialists. The sine qua non of successful evaluation and management is a common understanding of pathogenesis, eg, lack of sensation and increased weight bearing on pressure points. Sensation level is assessed grossly with a cotton Q-tip on the toe pads, metatarsal heads, instep, and heel of the supine patient. The patient then sits with foot rested on the opposite knee and is asked to localize the area of perceived touch. Often some sensation will be intact, but the patient will not be able to localize the site of touch. A more precise and predictive indicator of sensory level is the nylon filament, which is applied to the plantar

aspect of the foot and bends at 10 grams of pressure. With eyes closed the patient indicates each time pressure is felt. Normal sensation levels detect 1 to 2 grams of pressure. Inability to sense 10 grams of pressure places a foot at considerable risk for ulceration.[7]

If pulses (femoral, popliteal, dorsalis pedis, posterior tibial) are not palpable or there are clinical signs of ischemia, noninvasive vascular evaluation is immediate, consisting of a Doppler study with attention to wave form and ankle brachial index. If the ankle pressure is higher than anticipated by the wave form, the patient likely has medical calcinoses. Toe photoplethysmography is used to better define distal runoff into the foot. Angiography is utilized to localize vessel occlusion and potential need for revascularization.

Treatment is never as effective as prevention, which is the ultimate goal in the reduction of lower extremity amputations. Foot care education must bring patients to an understanding of their disease and a knowledge of why ulcers occur. At-risk patients receive a basic foot care handout that stresses daily inspection of the feet for redness, swelling, or calluses, and the need to consult a physician for any changes in the feet. Footwear is crucial both in the prevention of ulcers and in the maintenance of an intact foot once an ulcer has healed. Localized pressures on the soles can be reduced by spreading stress over the whole surface of the sole and for most diabetics, this can be accomplished by running shoes[8] with molded inserts. For a severely deformed Charcot foot, a soft leather molded shoe might be required. However, shoe sizes change as neuropathy alters muscles and bones and a correctly fitted shoe might be ill-fitting and even harmful in the future. Daily examination for new areas of erythema or callus, indicative of new pressure sites, is critical.

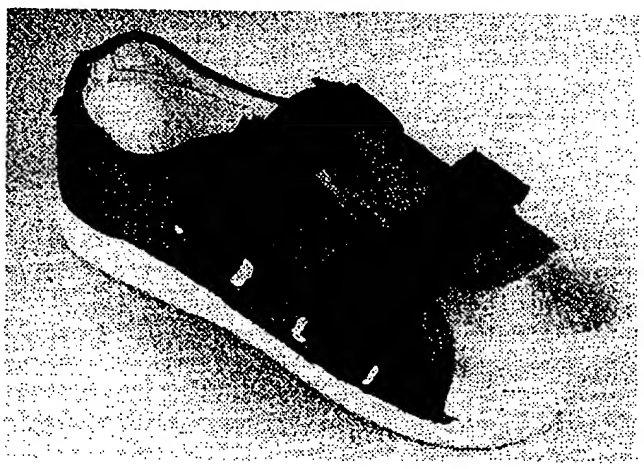
If an ulcer is present, two aspects of therapy are absolutely essential for healing: thorough debridement and total relief from pressure on the ulcer site. All neuropathic ulcers are debrided aggressively and promptly without anesthesia in the clinic. Necrotic tissue and callus must be completely excised to provide a clean ulcer base in preparation for granulation tissue and reepithelialization. Enzyme preparations and wet-to-dry methods do not substitute for thorough mechanical debridement. Total relief from pressure can be difficult to accomplish. Patients do not realize that just a few steps in bare feet or in nonsupporting soft slippers can damage the reepithelializing ulcer bed. Insensate patients should never go barefoot. Despite crutches, orthoses, and instruction, some pressure on the ulcer seems inevitable. Relief from pressure can be effected by total contact casting that protects the foot, distributes stress, and allows the patient to be mobile and continue with some daily activities (Figure 3). Casts can be applied for periods of 3 to 6 weeks but only after ulcers are free of infection with a clean ulcer bed.[6] Our modified technique of casting, a three layered gel-plaster-glass method, provides the healing quality of the gel cast, the solid structure of the plaster cast, and fiberglass for additional protection and immediate ambulation.

If a total contact cast cannot be applied, a healing shoe or a rocker orthosis might be effective. Healing shoes (Figure 4) and orthoses with molded inserts of Plastazote to fit the ulcerated foot do not remove or distribute pressures as effectively as the contact casts. Patients must always wear only the prescribed footwear with even one or two step ambulation.

The role of infection is controversial. The clinical appearance generally dictates the use of antibiotics. Most superficial ulcers without inflammatory signs of erythema, warmth, and fluctuance will not require antibiotic therapy. Cellulitis or signs of deep soft tissue foot infection require hospitalization with intravenous antibiotics and bed rest. Tissue necrosis and fetid odor suggest anaerobic infection. Deep foot infection with abscess formation requires aggressive debridement, incision, and marsupialization to allow adequate drainage. Antibiotic therapy never supplants the need for drainage and debridement of an infected foot and will frequently fail if the wound is not opened. Cultures from foot ulcers will often be polymicrobial and unreliable if a superficial swab is taken from the ulcer bed or through the ulcer. More reliable methods for obtaining cultures include: aspiration of fluctuant or bullous areas, swabs of expressible purulent drainage, or biopsy. Many uncomplicated infected superficial ulcers will grow gram positive cocci and can be treated on an outpatient basis.[9]

The x-ray image changes of diabetic osteopathy—demineralization, resorption, and fractures—must be distinguished from osteomyelitis to reduce unnecessary

Figure 3. Healing shoe with molded Plastazote insole.



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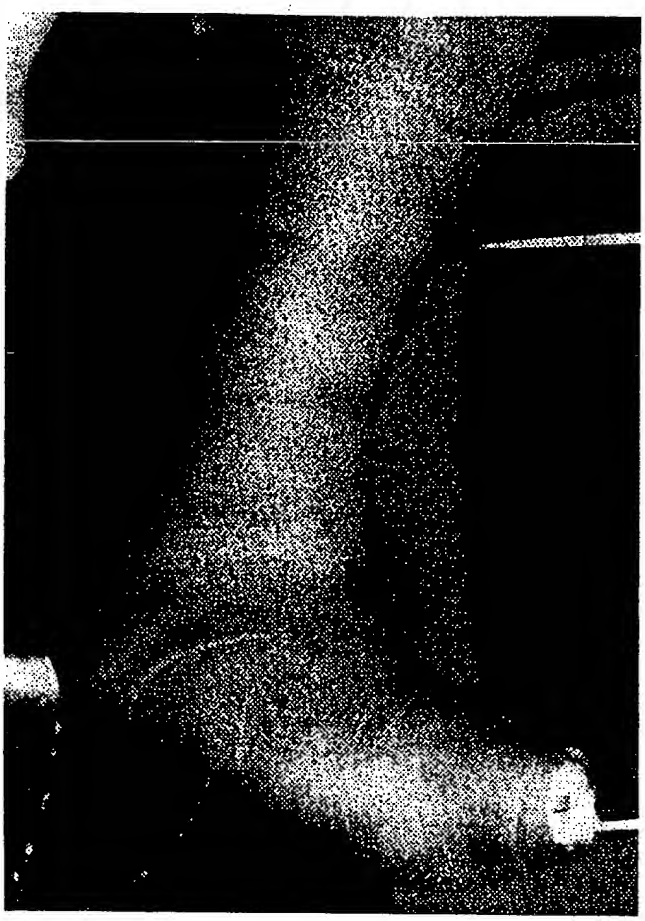

Figure 4. Walking contact gel-plaster-glass cast

antibiotic therapy and amputations. This distinction can often be difficult even with scans and magnetic resonance imaging.[10–12] Bone exposed in ulcers is likely to become infected. Shards of bone in the ulcer should be removed and any soft infected exposed bone cut back with a rongeur to healthy, vigorously bleeding, intact bone.

Wound care adheres to the application of basic principles after the ulcer has been thoroughly debrided. Wet-to-dry saline dressings play little role in a clean wound and damage the new epithelium. The clean healing ulcer should remain quiescent with avoidance of too frequent manipulation either from outside pressures or too frequent or toxic dressings. Povidone iodine, peroxide, and other antiseptics can be toxic to fibroblasts and should be avoided.[13] Because a moist environment promotes re-epithelialization, desiccation and eschars impede the epithelialization process and must be prevented. Continuous moist saline dressings can provide an optimal environment for healing. Topical antibiotic ointments, eg, mupirocin with antistaphylococcal activity prevents desiccation of the wound base. Benzoyl peroxide promotes a moist antiseptic wound bed and might also stimulate granulation tissue.[14] Growth factors, not yet generally available, attract fibroblasts and other cells involved in the early phases of wound healing.[15] Trials with topical preparations are difficult to evaluate in diabetic foot ulcers because of the inability to keep the area pressure free during the study period unless bed rest is imposed.

Because dry, fissured skin is more prone to ulceration, the insensate foot skin should be kept soft and pliable with petrolatum or other emollients. Petrolatum, used as an emollient, penetrates to all levels of the stratum corneum and provides protection in the form of an impermeable barrier.[16] If suspected, tinea pedis should be confirmed mycologically and treated aggressively.

Wound dressings should be as thin as possible because a foot with bulky dressings forced into a shoe can create new pressure points and render molded inserts ineffective. If an ulcer requires bulky dressings, casting or special orthoses are likely indicated.

Occlusive opaque dressings have not been generally acceptable on insensitive sites that bear pressure. Neither patient nor caretaker can visualize on a day-to-day basis any changes in the wound. Because pressure and friction are difficult to control in the insensate foot, maceration with extension of the ulceration can occur beneath the dressing.

Despite medical and mechanical therapy, some neuropathic ulcers do not heal or become infected. Bone-removing surgery might be the necessary therapeutic option, but the surgical focus is always the optimal restitution of weight bearing. As bones are removed, new potentially dangerous sites of weight bearing can be created.

Attention must be given to the newly healed diabetic foot ulcer. The shear stresses of walking can tear a fragile, new inflexible scar. Therefore, the patient should learn to take short steps in well fitted shoes with molded insoles and should make any lifestyle changes necessary to prevent recurrence or new ulcers on other sites.[6]

Most ulcers on the diabetic foot can be healed and amputations prevented if physicians teach preventive foot care and treat ulcers based on an understanding of the types and etiology of ulcers and basic principles of wound care.

References

1. Diabetes Surveillance, 1980–1987, US Dept of Health and Human Services, The Division of Diabetes Translation 1990;23–5.
2. Bild DE, Selby JV, Sinnock P, Bronner WS, Braveman P, Showstack JA. Lower-extremity amputation in people with diabetes: epidemiology and prevention. Diabetes Care 1989;12:24–31.

3. Mills JL, Beckett WC, Taylor SM. The diabetic foot: consequences of delayed treatment and referral. Southern Med J 1991;84:970–4.
4. Sanders LJ, Frykberg RG. Diabetic neuropathic osteoarthropathy: the charcot foot. In: Frykberg RGG, ed. The High Risk Foot in Diabetes Mellitus. New York: Churchill Livingstone, 1991.
5. LoGerfo FW, Coffman JD. Vascular and microvascular disease of the foot in diabetes. N Engl J Med 1984;311:1615–9.
6. Brand PW. The diabetic foot. In: Ellenberg M, Rifkin H, eds. Diabetes Mellitus: Theory and Practice. New York: Medial Examination Publishers, 1983.
7. Duffy JC, Patout CA. Management of the insensitive foot in diabetes: lessons learned from Hansen's disease. Military Medicine 1990;155:575–9.
8. Soulier SM. The use of running shoes in the prevention of plantar diabetic ulcers. J Am Podiatr Med Assoc 1986; 76:395–400.
9. Lipsky BA, Pecoraro RE, Larson SA, et al. Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Arch Intern Med 1990;150:790–7.
10. Zlatkin MD, Pathria M, Sartoris DJ, et al. The diabetic foot, diagnostic imaging in bone disease. Radiol Clin North Am 1987;25:1095–105.
11. Newman LG, Waller J, Palestro CJ, et al. Unsuspected osteomyelitis in diabetic foot ulcers. JAMA 1991;266: 1246–51.
12. Moore TE, Yuh WTC, Kathol MH, El-Khoury GY, Corson JD. Abnormalities of the Foot in Patients with Diabetes Mellitus: Findings on MR Imaging. AJR 1991;157:813–816.
13. Lineaweaver W, Howard R, Souay D, et al. Topical antimicrobial toxicity. Arch Surg 1985;120:267–70.
14. Lynch WS, Bailin PL. The promotion of wound healing following chemosurgery (Mohs technique) by dressings with a lotion of benzoyl peroxide. J Dermatol Surg Oncol 1978;4:91–5.
15. Keyser JE. Foot wounds in diabetic patients. Postgrad Med 1991;91:98–109.
16. Ghadially R, Halkier-Sorensen L, Elias PM. Effects of petrolatum on stratum corneum structure and function. J Am Acad Dermatol 1992;26:387–96.